



journal homepage: www.elsevier.com/locate/jjcc



Original article

What variables were associated with the inducibility of ventricular fibrillation during electrophysiologic stimulation test in patients without apparent organic heart disease?

Naoki Sugi (MD)^a, Akihiko Shimizu (MD, FJCC)^{b,*}, Takeshi Ueyama (MD)^a,
Yasuhiro Yoshiga (MD)^a, Masahiro Doi (MD)^a, Toshihide Ohmiya (MD)^a,
Makoto Ohno (MD)^a, Masaaki Yoshida (MD)^a, Masunori Matsuzaki (MD, FJCC)^a

^a Division of Cardiology, Department of Medicine and Clinical Science, Yamaguchi University Graduate School of Medicine, Yamaguchi, Japan

^b Faculty of Health Sciences, Yamaguchi University Graduate School of Medicine, 1-1-1 Minami-Kogushi, Ube, 755-8505 Yamaguchi, Japan

Received 19 November 2009; received in revised form 28 January 2010; accepted 29 January 2010

Available online 1 March 2010

KEYWORDS

Electrophysiology;
Ventricular
fibrillation;
Sudden death;
Syncope

Summary

Objective: The purpose of our study was to determine what variables were associated with ventricular fibrillation (VF) induced during electrophysiological stimulation test in patients without apparent organic heart disease.

Methods: Our study evaluated 77 patients (51 ± 15 years) who underwent electrophysiological stimulation test, signal averaging, and Na⁺ channel-blocker challenge test (pilsicainide test). The subjects were divided into two groups, the Brugada group and non-Brugada group. Further, the patients were divided into three subgroups on the base of symptoms (8, 7 symptomatic; 9, 13 syncope; 28, 12 asymptomatic group; in the Brugada and non-Brugada groups, respectively). Multivariate analyses evaluated the association between baseline clinical factors and the induction of VF.

Results: The inducibility of VF was significantly ($p < 0.0001$) higher in the Brugada group ($n = 33$, 73%) than the non-Brugada group ($n = 4$, 13%). The multivariate analysis demonstrated that symptoms (odds ratio (OR) 31.6; 95% confidence interval (CI): 2.3–430.6; $p < 0.01$), type 1 electrocardiogram after pilsicainide test (OR 21.3; CI: 1.7–272.2; $p < 0.02$), and syncope (OR 13.5; CI: 1.2–158.8; $p < 0.05$) were strongly associated with the inducibility of VF, but not with family history, type 1 electrocardiogram in control, positive in late potential, max Δ ST elevation ($\geq 200 \mu\text{V}$) after pilsicainide test.

* Corresponding author. Tel.: +81 836 22 2856; fax: +81 836 22 2856.
E-mail address: ashimizu@yamaguchi-u.ac.jp (A. Shimizu).

Conclusions: The symptoms, syncope, and type 1 electrocardiogram after pilsicainide test were independently associated with the electrophysiological substrate of VF in patients without apparent heart disease.

© 2010 Published by Elsevier Ireland Ltd on behalf of Japanese College of Cardiology.

Introduction

Ventricular fibrillation (VF) is one of the important etiologies of sudden cardiac death and occurs commonly in patients with organic heart disease and left ventricular dysfunction. However, VF occurs even in patients without apparent heart disease, which is so-called idiopathic ventricular fibrillation. Recently, idiopathic VF has been classified as Brugada syndrome [1–7], long QT syndrome [8], short QT syndrome [9], and catecholaminergic polymorphic ventricular tachycardia [10], and others, based on their specific clinical characteristics.

Brugada syndrome is a relatively frequent disease associated with VF in patients without apparent heart disease in Japan and Asia [5]. It is also associated with electrocardiographic abnormality of the right bundle branch block with ST elevation in the right precordial leads [1–7]. The electrocardiogram (ECG) findings are the most useful parameters for the diagnosis of the Brugada type ECG [5]. Furthermore, the Na⁺ channel-blockers challenge test is also useful because it can unmask the Brugada type ECG and induce the elevation of the ST-segment in patients with intermittent or concealed Brugada syndrome [5,6].

Although several parameters, such as the ECG findings, electrophysiological stimulation test (EPS), signal averaging, T-wave alternance (TWA), and abnormal genes have been reported to be predictive values for sudden cardiac death [7,11–15], the specificity of the induction test of VT (ventricular tachycardia)/VF during EPS remains unclear [13,14]. Since there is a wide variation in the incidence of events [7,16,17], the appropriate risk stratification for sudden cardiac death remains uncertain. A recently published second consensus report on the Brugada syndrome [18] from Europe and the USA implied that patients with either spontaneous or drug-induced type 1 Brugada ECG and a history of syncope or sudden cardiac death should have an implantable cardioverter defibrillator (ICD) implanted. Asymptomatic patients with a spontaneous type 1 Brugada ECG or asymptomatic patients with a drug-induced type 1 Brugada ECG and a family history of sudden cardiac death should undergo EPS to guide the selection of patients for ICD implantation.

In Japan, the inducibility of VF is one of the factors to make a decision of implantation of ICD according to the guidelines on ICD [19] or Brugada syndrome [20]. It is presumed that the inducibility of VF in patients without apparent organic heart disease indicates the existence of VF substrate. However, it is still unclear what variables are associated with VF induced during EPS in patients without apparent organic heart disease. Therefore, we performed a multivariate analysis to clarify what variables were strongly related to the inducibility of VF in patients without any apparent organic heart disease.

Methods

Subjects

Our study evaluated 77 patients who underwent EPS for the diagnosis of arrhythmia, risk stratification in Brugada syndrome, and/or sudden cardiac death in patients with no apparent heart disease and normal left ventricular function between January 2005 and August 2008. In addition, they underwent ECGs, Na⁺ channel-blocker challenge tests, signal averaging, coronary angiography, and cardiac echocardiography during their hospitalization. Patients with idiopathic ventricular tachycardia (Ca antagonist sensitive) [21], long QT syndrome [8], short QT syndrome [9], and catecholaminergic polymorphic ventricular tachycardia [10] were excluded. Furthermore, those with spontaneous VF induced by ischemia, electrolyte disturbance, and/or hypothermia were also excluded.

A diagnosis of Brugada type ECG was made based on the following criteria: (1) J point amplitude over 0.2 mV with either spontaneous or drug-induced type 1 ECG (coved type ST elevation) in at least two of the three right precordial leads in the standard right precordial leads (V1–V3), or one or two intercostal spaces above the standard right precordial leads. Three types of repolarization patterns were defined as type 1, type 2, and type 3 according to the consensus report [5]. Type 1 is characterized by a prominent coved ST-segment elevation displaying J wave amplitude ≥ 2 mm. Type 2 also has a high take-off ST-segment elevation, but in this case J wave amplitude (≥ 2 mm) gives rise to a gradually descending ST-segment elevation (remaining ≥ 1 mm above the baseline), followed by a positive or biphasic T-wave that results in a saddle back configuration. Type 3 has a J wave amplitude (≥ 2 mm) that gives rise to (1) a gradually descending ST-segment elevation (remaining < 1 mm above the baseline), followed by a positive T-wave that results in a saddle back configuration; (2) normal findings on physical examination; (3) no abnormality in either right or left ventricular morphology and/or function demonstrated by chest radiography and echocardiography; (4) absence of other factors, such as ischemia, electrolyte disturbance, or hypothermia that may have caused the ST-segment abnormality.

Since the criteria of ECG on Brugada syndrome in our study was that J point amplitude over 0.2 mV with either spontaneous or drug-induced type 1 ECG (coved type ST elevation) in at least two of the three right precordial leads (V1–V3) in the standard right precordial leads (V1–V3), or one or two intercostal spaces above the standard right precordial leads, we excluded the patients who had type 2 or type 3 ECG in control state and then showed still type 2 or type 3 ECG even after pilsicainide test. Therefore, the non-Brugada group included eight patients who had type 2

or type 3 ECG in control state and then showed still type 2 or type 3 ECG even after pilsicainide test, or many patients who had type 1, type 2, or type 3 repolarization pattern with J point amplitude less than 0.2 mV, because they were introduced to our hospital for the suspicion of Brugada syndrome with unknown etiology of palpitation attack.

The subjects were divided into two groups, the Brugada group and non-Brugada group. In addition, the subjects were divided into three subgroups: (1) the symptomatic group included patients that had a history of documented lethal VT or VF, or aborted sudden cardiac death; (2) the syncope group included patients who had episodes related to brain ischemia such as syncope or fainting, but no documented arrhythmias at that time; and (3) the asymptomatic group included patients who had no episodes of documented lethal ventricular arrhythmia and/or syncope.

All patients then underwent echocardiography while careful attention was paid to right ventricular enlargement and/or wall motion abnormalities. Therefore, patients with apparent organic heart disease or other factors that may have influenced ST-segment elevation were excluded. All patients provided their written informed consent to participate in the study, which was approved by the Institutional Clinical Research and Ethics Committee.

Na⁺ channel-blocker challenge test (pilsicainide test)

Na⁺ channel-blocker challenge tests were performed using pilsicainide, as previously reported [6]. Pilsicainide was administered intravenously at 1 mg/kg/over 10 min with continuous ECG and non-invasive blood pressure monitoring. During drug administration, 12-lead ECG was recorded and then the standard right precordial leads (V1–V3), and 3 leads at 1 intercostal space higher than the standard right precordial leads were recorded using the V4-6 electrodes. Drug administration was immediately stopped when ST-segment elevation (>5 mm), extensive QRS prolongation (>0.12 s), unfavorable symptoms, and/or frequent ventricular arrhythmias were observed. The test was considered positive if the coved type ECG pattern (type 1 ECG) appeared in more than one right precordial lead.

Electrocardiography

Standard 12-lead ECG (ECG-9322, Nihon Kohden Corp., Tokyo, Japan) was recorded before and after the administration of pilsicainide, as previously reported [6]. The J wave amplitude (μ V) was analyzed by an organized computer algorithm (ECAPS 12C, Nihon Kohden). In the ECAPS 12C, the terminal point of the QRS (J point) was defined as the offset point of the QRS waveform determined from the averaged QRS waveforms from the 12 leads. After the drug test, the increase in the ST-segment (Δ ST elevation) was calculated in each of the standard right precordial leads (V1–V3), one, or two intercostals space above the standard right precordial leads. The maximum Δ ST elevation was defined as the max Δ ST elevation.

Signal averaging

Signal averaging was performed using the signal-averaged ECG (Fukuda Denshi Co. Ltd., FDX-6531, Tokyo, Japan). A positive late potential was considered when two of three criteria (F-QRS >135 ms, or LAS40 >39 ms, or RMS40 <15 μ V) were fulfilled.

Electrophysiological stimulation test

The EPS was performed in the fasting state, and all previous antiarrhythmic agents had been discontinued for at least five half-lives. An intravenous propofol infusion was used to achieve general anesthesia.

Recordings. A standard 5F decapolar catheter with ten 2-mm width electrodes and a 2-mm inter-electrode spacing was introduced via the right femoral vein or left or right subclavian veins. The catheters were positioned in the high lateral right atrium, His bundle region, coronary sinus, right ventricular (RV) apex and RV outflow tract. The 12 lead surface ECG leads were recorded simultaneously with the intracardiac electrograms. The bipolar endocardial electrograms were recorded from each of the five closely spaced bipolar pairs of electrodes filtered through a 30–400 Hz filter with a sampling interval of 1 kHz using a computed electric recorder (Cardio LAB v51D, GE Medical Systems, Milwaukee, WI, USA).

Stimulation protocol. Programmed electrical stimulation was delivered at twice the diastolic threshold at a 2-ms pulse width. The stimulation protocol for our study included up to 3 extrastimuli delivered during pacing at drive cycle lengths of 600 and 400 ms with a minimum coupling interval of S₂S₃ 180 ms at two extrastimuli and of S₂S₃ and S₃S₄ 200 ms at three extrastimuli, and rapid pacing down to a cycle length of 240 ms or 2:1 ventricular response from the RV apex and/or RV outflow tract.

When the induced VF lasted for several seconds, we started preparing for cardioversion. Then, the energy was discharged after the delivered energy was fulfilled. The results of the EPS were considered positive only when VF or sustained ventricular tachycardia lasting 30 s induced.

Statistical analysis

The data are presented as the mean \pm SD. The ECG data were analyzed by paired *t*-test. The chi-square test for independence was used for comparisons of the prevalence. A tested analysis of variance (ANOVA) with the Bonferroni test was used to compare consecutive data among subgroups. The chi-square test and Student *t*-test for independent variables were used for comparisons among groups. The univariate analysis (Mantel-Haenszel method) and the multivariate analyses (linear model method) were performed the software (SPSS 16.0 Family for Windows, Mapinfo, Troy, NY, USA) to evaluate the association between clinical factors and the induction of VF. These analyses tested only main categories [symptoms, syncope, family history, type 1 ECG in control, positive in late potential, type 1 ECG after pilsicainide test, and max Δ ST elevation (\geq 200 μ V) after pilsicainide test]. A value of *p* < 0.05 was considered to be statistically significant.

Results

Clinical characteristics of the subjects

The study enrolled 77 patients (51 ± 15 years). The ratio of males to females was 8.6 (69/8) in all subjects (Table 1). There was no significant difference in the age (53 ± 14 years vs. 48 ± 15 years) or gender (male/female, 42/3 vs. 27/5) between the Brugada group and the non-Brugada group. A family history was observed in 22% (10/45) of the Brugada group and 9% (3/32) of the non-Brugada group, but it did not reach a significant difference ($p = 0.13$) between the two groups.

There were 45 subjects in the Brugada Group and 32 in the non-Brugada group. The Brugada group contained 8 in the symptomatic group, 9 in the syncope group and 28 in the asymptomatic group, and the non-Brugada group contained 7 in the symptomatic group, 13 in the syncope group and 12 in the asymptomatic group (Table 1).

The ratio of males to females in the comprised symptomatic patients (symptom/syncope group) of the Brugada group (17/0) was significantly higher than those of the non-Brugada group (16/4; $p = 0.05$).

There was no significant intra-group difference on the incidence of family history in either the Brugada or the non-Brugada group (Table 1).

One patient with symptoms in the non-Brugada group showed a type 2 ECG in control state and then still showed type 2 ECG even after pilsicainide test. Further, another patient with symptoms in the non-Brugada group had type 2 repolarization patterns ECG with J point amplitude less than 0.2 mV even after pilsicainide test (max Δ ST elevation $140 \mu\text{V}$). Interestingly, VF was induced during EPS in both patients. The other five patients with symptoms in the non-Brugada group had no induction of VF.

Electrophysiological findings of subjects

In the Brugada group, type 1 ECG was observed in 44% of the subjects (20/45) and types 1–3 ECG (the repolarization pattern of type 1, type 2, or type 3 was shown in ECG) was seen in 60% (27/45) in the control state. Type 1 ECG was observed in 100% of the patients (45/45) after pilsicainide test and types 1–3 ECG was also observed in 100%. In the non-Brugada group, five patients (1 symptoms, 1 syncope, and 3 asymptomatic) with type 2 or 3 ECG in the control did not show type 1 ECG after pilsicainide test. Thus, those five patients belonged to the non-Brugada group in our study.

The max Δ ST elevation ($\geq 200 \mu\text{V}$) was seen in 84% (38/45) of the Brugada group, but 0% of the non-Brugada group. Positive of late potential was observed in 64% (29/45) of the Brugada group and 25% (8/32) of the non-Brugada group, and there was a significant difference ($p = 0.0005$).

There were no significant differences in the incidence of type 1 ECG and types 1–3 ECG in the control and those after pilsicainide test, the max Δ ST elevation and positive in late potential among the subgroups of patients with Brugada syndrome (Table 2).

Table 1 Clinical characteristics of the subjects.

	Brugada group (n = 45)				Non-Brugada group (n = 32)			
	Symptom ^a n (%)	Syncope ^a n (%)	Asymptom ^a n (%)	Test for intra-group (p)	Symptom ^a (%)	Syncope ^a (%)	Asymptom ^a (%)	Test for intra-group (p)
Number of patients	8	9	28		7	13	12	–
Symptoms	+	–	–		+	–	–	
Syncope	–	+	–		–	+	–	
Age (years)	53 ± 17	51 ± 17	54 ± 14	0.89	43 ± 13	49 ± 14	51 ± 15	0.55
Gender (male/female)	8/0	9/0	25/3	0.38	5/2	11/2	11/1	0.50
Family history	4 (50)	2 (22)	4 (14)	0.10	0 (0)	1 (8)	2 (17)	0.47

Symptoms: documented VF and/or aborted sudden cardiac death; syncope: syncope from unknown etiology; VF, ventricular fibrillation.
^a Subgroup.

Table 2 Clinical characteristics and electrophysiological findings of the subjects.

	Brugada group (n = 45)				Non-Brugada group (n = 32)			
	Symptom ^a n (%) n = 8	Syncope ^a n (%) n = 9	Asymptom ^a n (%) n = 28	Test for intra-group (p)	Symptom ^a n (%) n = 7	Syncope ^a n (%) n = 13	Asymptom ^a n (%) n = 12	Test for intra-group (p)
Type 1 ECG in control	5 (56)	3 (33)	12 (43)	0.46	0 (0)	0 (0)	0 (0)	—
Types 1–3 ECG in control	6 (75)	4 (44)	17 (61)	0.44	1 (14)	1 (8)	3 (25)	0.49
Type 1 ECG after pilsicainide test	8 (100)	9 (100)	28 (100)	—	0 (0)	0 (0)	0 (0)	—
Types 1–3 ECG after pilsicainide test	8 (100)	9 (100)	28 (100)	—	1 (14)	3 (23)	3 (25)	0.85
MaxΔST elevation ($\geq 200 \mu\text{V}$)	6 (75)	8 (89)	24 (86)	0.70	0 (0)	0 (0)	0 (0)	—
Positive in late potential	6 (75)	7 (78)	16 (58)	0.31	1 (14)	4 (31)	3 (25)	0.70
ERP								
RV apex at BCL 600 ms (ms)	247 ± 6	233 ± 13	241 ± 14	0.21	246 ± 24	244 ± 17	244 ± 21	0.98
RV apex at BCL 400 ms (ms)	230 ± 10	210 ± 8	221 ± 11	0.02	222 ± 19	224 ± 16	219 ± 22	0.82
RV outflow tract at BCL 600 ms (ms)	237 ± 15	228 ± 17	235 ± 11	0.43	255 ± 31	243 ± 18	236 ± 18	0.35
RV outflow tract at BCL 400 ms (ms)	237 ± 12	211 ± 16	225 ± 15	0.05	225 ± 31	225 ± 18	227 ± 20	0.96
Induction of VF	8 (100)	8 (89)	17 (60)	0.04	1 (14)	3 (23)	0 (0)	0.22

There was no significant difference in ERP in the RV apex or in the RV outflow at BCLs 600 and 400 ms between the Brugada group and the non-Brugada group. Types 1–3 ECG: the repolarization pattern of type 1, type 2, or type 3 was shown in ECG. Asymptom, asymptomatic; ECG, electrocardiogram; ERP, effective refractory period; RV, right ventricle; BCL, basic cycle length; VF, ventricular fibrillation.

^a Subgroup.

Table 3 Incidence and univariate analysis for the induction of ventricular fibrillation in the control study.

Variables	n	Incidence Number of patients with induced VF (%)	Univariate analysis		
			OR	95% Confidence intervals	p
Symptoms	15	10 (67)	2.28	0.70–7.43	0.173
Syncope	22	11 (50)	0.96	0.36–2.59	0.943
Family history	13	8 (62)	1.70	0.50–5.77	0.392
Type 1 ECG in control	20	16 (80)	5.91	1.75–19.96	0.004
Positive in late potential	37	25 (68)	3.87	1.50–9.97	0.005
Type 1 ECG after pilsicainide test	45	34 (76)	16.69	5.17–53.87	0.0001
Max Δ ST elevation ($\geq 200 \mu\text{V}$)	38	30 (79)	12.50	4.25–36.75	0.0001

Symptoms: documented VF and/or aborted sudden cardiac death; syncope: syncope from unknown etiology; VF, ventricular fibrillation; OR, Mantel-Haenszel odds ratio; ECG, electrocardiogram.

Electrophysiological stimulation test in subjects in the control state

EPS was performed in all subjects. There was no significant difference of the ERP in the RV apex at BCL 600 ms (239 ± 13 ms vs. 245 ± 20 ms) and 400 ms (220 ± 14 ms vs. 220 ± 17 ms) between the Brugada group and non-Brugada group. Furthermore, there was no significant difference in the ERP in the RV outflow tract at BCL 600 ms (234 ± 15 ms vs. 242 ± 20 ms) and 400 ms (222 ± 17 ms vs. 226 ± 20 ms) between the Brugada group and non-Brugada group. There was no significant difference in the ERP in the RV apex and RV outflow tract at BCL 600 and 400 ms among the subgroups of the Brugada group as well as those of the non-Brugada group (Table 2).

Induction of VF. VF was induced in 73% (33/45) of patients in the Brugada group and 13% (4/32) of patients in non-Brugada group. Inducibility of VF was significantly ($p < 0.0001$) higher in Brugada syndrome than non-Brugada syndrome.

In the Brugada group with induction of VF ($n = 33$), VFs were induced by single ventricular extrastimuli ($n = 0$, 0%) and double ventricular extrastimuli ($n = 15$, 45%) from RV apex and/or RV outflow tract. Further, VFs were induced by triple ventricular extrastimuli ($n = 18$, 55%). VFs were more frequently ($p = 0.009$) induced by pacing from RV outflow tract ($n = 27$, 82%) than from RV apex ($n = 17$, 52%) and they were induced by triple ventricular extrastimuli from both pacing sites ($n = 11$, 33%).

In the non-Brugada group with induction of VF ($n = 4$), VFs were induced by single ventricular extrastimulation ($n = 1$, 25%) and double ventricular extrastimuli ($n = 1$, 25%) from RV apex and/or RV outflow tract. Further, VFs were induced by triple ventricular extrastimuli ($n = 2$, 50%) from the RV apex ($n = 1$, 25%), RV outflow tract ($n = 2$, 50%), and both pacing sites ($n = 1$, 25%). Note that the inducibility of VF was significantly ($p = 0.04$) different among the subgroups in the Brugada group, but not the non-Brugada group. The inducibility of VF (94%, 16/17) in comprised symptomatic patients (symptomatic and syncope group) of the Brugada group was significantly ($p = 0.008$) higher than that (61%, 17/28) in the asymptomatic group of those with Brugada syndrome.

A univariate test was conducted on the clinical examinations for induction of VF and those results are shown in

Table 3. Type 1 ECG after pilsicainide test, the max Δ ST elevation ($\geq 200 \mu\text{V}$), type 1 ECG in control, and positive in late potential had relatively high odds ratios and significance values. However, the multivariate analysis using the linear regression model evaluated the association between baseline clinical factors and the induction of VF. The results are displayed in Table 4, including the odds ratios and 95% confidence intervals. Symptoms indicated the highest odds ratio (odds ratio 31.6; 95% confidence interval: 2.3–430.6; $p = 0.01$) followed by type 1 ECG after pilsicainide test (odds ratio 21.3; 95% confidence interval: 1.67–272.3; $p = 0.02$). Syncope (odds ratio 13.5; 95% confidence interval: 1.2–158.8; $p = 0.04$) also was a significant variable associated with induced VF. However, a family history of sudden cardiac death, type I ECG in the control, positive of late potential, and max Δ ST elevation ($\geq 200 \mu\text{V}$) did not show significant association with induction of VF.

Follow-up study

ICDs were implanted in 18 patients in the Brugada group (9 symptomatic group, 6 syncope group, 3 asymptomatic group) and in 4 in the non-Brugada group (1 symptomatic, 3 syncope, 0 asymptomatic group). Appropriate shock was delivered in only one patient of the symptomatic group in the Brugada group during the average observation period of 43 ± 14 months. No appropriate shock was delivered to the rest of the patients.

Discussion

Subjects

The subjects in the current study underwent EPS for the diagnosis of Brugada syndrome or risk stratification for patients who had a family history of Brugada syndrome and for the further examination of Brugada-like ECG and/or palpitation and/or syncope. The standard right precordial leads (V1–V3) and an additional six right precordial leads that were located one or two intercostal spaces above the standard right precordial leads (V1–V3) were used for the diagnosis of Brugada type ECG because some patients showed type 1 ECG in additional leads even when normal ECGs were seen in the standard right precordial leads

Table 4 Multivariate analysis for the induction of ventricular fibrillation in the control study.

Variables	n	Multivariate analysis		
		OR	95% Confidence intervals	p
Symptoms	15	31.6	2.3–430.6	0.01
Syncope	22	13.5	1.2–158.8	0.04
Family history	13	0.4	0.06–2.8	0.37
Type 1 ECG in control	20	1.3	0.3–6.7	0.76
Positive in late potential	37	1.9	0.5–7.4	0.36
Type 1 ECG after pilsicainide test	45	21.3	1.7–272.3	0.02
Max Δ ST elevation ($\geq 200 \mu\text{V}$)	38	5.9	0.7–39.3	0.11

Symptoms: documented VF and/or aborted sudden cardiac death; syncope: syncope from unknown etiology; OR, odds ratio; ECG, electrocardiogram.

(V1–V3) [6]. A Na⁺ channel-blocker challenge test using pilsicainide can unmask intermittent or concealed Brugada type ECG. However, there is still controversy regarding whether these drugs are specific for Brugada syndrome. Thus, in our study, only type 1 ECG was regarded as Brugada type ECG after the Na⁺ channel-blocker challenge test to avoid an overestimate of Brugada syndrome.

Our study showed Brugada syndrome was more common in males (male:female = 12:1), however, there was no significant difference between the Brugada group and non-Brugada group.

Family history may be one of the major risk factors for sudden cardiac death in patients with Brugada syndrome. In our study, in 22% of the Brugada group had a family history while 9% of the non-Brugada group did as well. However, there was no significant difference in the prevalence of family history among the subgroups of the Brugada group. This may suggest that family history has a relatively weaker relationship with the risk of fatal cardiac events than expected, which is consistent with the findings of a meta-analysis of prognostic studies of patients with Brugada syndrome [22]. Gehi et al. [22] suggested that a history of syncope or sudden cardiac death, the presence of a spontaneous type 1 Brugada ECG, and male gender predict a more malignant natural history. They did not recommend the use of a family history of sudden cardiac death, the presence of an SCN5A gene mutation, or EPS to guide the management of patients with a Brugada ECG.

Recently, the Brugada syndrome investigators in Japan [23] reported that the long-term prognosis of probands in non-type 1 group was similar to that of type 1 group and that the presence of early repolarization was also a predictor of poor outcome, which included only probands with Brugada-pattern ST-elevation. Note that the criteria of Brugada syndrome in this study was J point amplitude more than 1 mm in the right precordial leads (V1–V3). Those findings suggested that it was difficult to discriminate high-risk patients only by using a standard 12 ECG. Further examination will be needed to solve this type of issue.

Electrophysiological characteristics in patients of Brugada syndrome

There were no significant differences in the incidence of type 1 ECG and the types 1–3 ECG in the control and those

after the pilsicainide test, max Δ ST elevation after pilsicainide test and positive in late potential among subgroups of patients with Brugada syndrome (Table 2). There was no significant difference in the ERPs at the RV apex and RV outflow tract at BCL 600 and 400 ms between the Brugada and non-Brugada groups, and among the subgroups of the Brugada group as well as those of the non-Brugada group.

The inducibility of VF was significantly higher in those with Brugada syndrome than the non-Brugada syndrome patients. This may suggest that the inducibility of VF is helpful in identifying individuals at risk of fatal cardiac events, as noted in previous reports [13,24,25]. However, recent large-scale studies [16,17,26] and a meta-analysis [22] on the prognostic studies of patients with Brugada syndrome did not support the usefulness of EPS. A low incidence of arrhythmic events was found in a large Brugada syndrome population [27], with an annual event rate of 2.6% during a follow-up of 3 years. The different results may be caused by the different methods in the stimulation protocol, end-point determination, and/or criteria for positive EPS.

The clinical implication of EPS for the risk stratification in patients with ischemic heart disease and low LV ejection fraction is relatively clear [28], but the usefulness of EPS for the risk stratification in patients with a Brugada ECG remains controversial [14,15]. Though the induction of VF during EPS suggests the existence of electrophysiological substrate of VF, the incidence of spontaneous VF is low in patients with induced VF in asymptomatic Brugada syndrome. One of the reasons is that the spontaneous VF in patients with Brugada syndrome depends mainly on the trigger factors rather than the existence of substrate. However, the existence of VF substrate is also important. Therefore, variables associated with VF induced during EPS in patients without apparent organic heart disease also important. If there is no VF substrate, the spontaneous VF never occurs. It is presumed that negative VF study indicated no risk of VF at that time.

Factors of VF induced by EPS

The univariate analysis indicated the induction of VF in patients without apparent heart disease had a relatively strong relation with type 1 ECG after pilsicainide test, max Δ ST elevation ($\geq 200 \mu\text{V}$) and type 1 ECG in control, because those factors had a relatively high incidence in patients with induction of VF. However, the patients in

our study had many complex backgrounds that have some effects on induction of VF. Therefore, we should use the multivariate analysis to determine what variables were independently associated with induction of VF during EPS in patients without organic heart disease.

A linear regression model was used to identify any independent predictors of the induction of VF during the stimulation test. In this manner, the independent predictive value of the relative risk to the induction of VF could be assessed. This analysis showed that symptoms (documented VF and/or aborted sudden cardiac death) had the highest odds ratio. This result is not inconsistent with the general consideration that a history of VF and/or aborted sudden cardiac death is the strongest variable to indicate the existence of substrate of VF in patients without apparent heart disease. Syncope also showed relatively higher odds ratio. This result is also not inconsistent with the general consideration.

Note that type 1 ECG after pilsicainide test also showed high odds ratio in a linear regression model, but not type 1 ECG in control. Type 1 ECG after pilsicainide test, itself, indicates the diagnosis of Brugada syndrome in our study, therefore, the diagnosis of Brugada syndrome itself is strong association with induction of VF during EPS in patients without apparent heart disease. Type 1 ECG after pilsicainide test is superior to type 1 ECG in control for the diagnosis of Brugada syndrome, because pilsicainide unmasks the concealed or intermittent Brugada syndrome. Since the odds ratio shows the relative risk, it is certain that type 1 ECG is important for the diagnosis of Brugada syndrome.

A family history of sudden cardiac death, type 1 ECG in control, positive of late potential, and $\max\Delta ST$ elevation ($\geq 200 \mu V$) and more did not have significant association with the induction of VF.

These findings suggested that symptoms, syncope, and type 1 ECG after pilsicainide test were independently associated with the electrophysiological substrate of VF in patients without apparent heart disease.

Study limitations

There were several limitations to our study. First, the sample sizes in each group were relatively small, because the subjects were divided into nine groups on the basis of Brugada type ECG and symptoms related to lethal ventricular events and/or brain ischemia. Second, long observation after EPS was not analyzed, because of infrequency of cardiac events. Third, a comprehensive genetic screening was not performed on all patients. Although this may have been ideal, genetic testing is of uncertain yield and is costly.

Conclusions

The electrophysiological characteristics of induced VF in patients without any apparent organic heart disease were assessed. The electrophysiological characteristics in patients with Brugada type ECG were a high inducibility of VF, relatively lower inducibility of VF in patients with asymptomatic patients, and no relationship with the family history. The multivariate analysis revealed that symptoms, syncope, and type 1 ECG after pilsicainide test were independently associated with the inducibility of VF.

References

- [1] Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death. A distinct clinical and electrocardiographic syndrome. *J Am Coll Cardiol* 1992;20:1391–6.
- [2] Brugada J, Brugada R, Brugada P. Right bundle-branch block and ST segment elevation in leads V1 through V3. A marker for sudden death in patients without demonstrable structural heart disease. *Circulation* 1998;97:457–60.
- [3] Brugada J, Brugada P. Further characterization of the syndrome of right bundle branch block. ST segment elevation, and sudden cardiac death. *J Cardiovasc Electrophysiol* 1997;8:325–31.
- [4] Brugada J, Brugada R, Antzelevitch C, Towbin J, Nademanee K, Brugada P. Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V1 to V3. *Circulation* 2002;105:73–8.
- [5] Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, Corrado D, Hauer RN, Kass RS, Nademanee K, Priori SG, Towbin JA, Study Group on the Molecular Basis of Arrhythmias of the European Society of Cardiology. Proposed diagnostic criteria for the Brugada syndrome: consensus report. *Eur Heart J* 2002;23:1648–54.
- [6] Ueyama T, Shimizu A, Yamagata T, Esato M, Ohmura M, Matsuzaki M, Kanemoto M, Kametani R, Sawa A, Suzuki S, Sugi N, Matsuzaki M. Different effect of the pure Na⁺ channel-blocker pilsicainide on the ST-segment response in the right precordial leads in patients with normal left ventricular function. *Circ J* 2007;71:57–62.
- [7] Brugada J, Brugada R, Brugada P. Determinants of sudden cardiac death in individuals with the electrocardiographic pattern of Brugada syndrome and no previous cardiac arrest. *Circulation* 2003;108:3092–6.
- [8] Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome. An update. *Circulation* 1993;88:782–4.
- [9] Gaita F, Giustetto C, Bianchi F, Wolpert C, Schimpf R, Riccardi R, Grossi S, Richiardi E, Borggrefe M. Short QT syndrome: a familial cause of sudden death. *Circulation* 2003;108:965–70.
- [10] Leenhardt A, Lucet V, Denjoy I, Grau F, Ngoc DD, Coumel P. Catecholaminergic polymorphic ventricular tachycardia in children. A 7-year follow-up of 21 patients. *Circulation* 1995;91:1512–9.
- [11] Kanda M, Shimizu W, Matsuo K, Nagaya N, Taguchi A, Suyama K, Kurita T, Aihara N, Kamakura S. Electrophysiologic characteristics and implications of induced ventricular fibrillation in symptomatic patients with Brugada syndrome. *J Am Coll Cardiol* 2002;39:1799–805.
- [12] Tatsumi H, Takagi M, Nakagawa E, Yamashira H, Yoshiyama M. Risk stratification in patients with Brugada syndrome: analysis of daily fluctuation in 12-lead electrocardiogram and signal-averaged electrocardiogram. *J Cardiovasc Electrophysiol* 2006;17:705–11.
- [13] Brugada P, Brugada R, Brugada J. Should patients with an asymptomatic Brugada electrocardiogram undergo pharmacological and electrophysiological testing. *Circulation* 2005;112:279–85.
- [14] Priori SG, Napolitano C. Should patients with an asymptomatic Brugada electrocardiogram undergo pharmacological and electrophysiological testing? *Circulation* 2005;112:285–91.
- [15] Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P, Potenza D, Moya A, Borggrefe M, Breithardt G, Ortiz-Lopez R, Wang Z, Antzelevitch C, O'Brien RE, Schulze-Bahr E, et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature* 1998;392:293–6.

- [16] Priori SG, Napolitano C, Gasparini M, Pappone C, Della Bella P, Giordano U, Bloise R, Giustetto C, De Nardis R, Grillo M, Ronchetti E, Faggiano G, Nastoli J. Natural history of Brugada syndrome: insight for risk stratification and management. *Circulation* 2002;105:1342–7.
- [17] Eckardt L, Probst V, Smits JPP, Bahr ES, Wolpert C, Schimpf R, Wichter T, Boisseau P, Heinecke A, Breithardt G, Borggrefe M, LeMarec H, Böcker D, Wilde AA. Long-term prognosis of individuals with right precordial ST-segment-elevation Brugada syndrome. *Circulation* 2005;111:257–63.
- [18] Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, Gussak I, LeMarec H, Nademanee K, Perez Riera AR, Shimizu W, Schulze-Bahr E, Tan H, Wilde A. Brugada syndrome: report of the second consensus conference—endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation* 2005;111:659–70.
- [19] Shimizu A. Cardiac resynchronization therapy with and without implantable cardioverter-defibrillator. *Circ J* 2009;73(Suppl. A):A29–35.
- [20] Ohe T, Aizawa Y, Atarashi H, Okumura K, Kasanuki H, Kamakura S. Guidelines for diagnosis and management of patients with long QT syndrome and Brugada syndrome. *Circ J* 2007;71(Suppl. IV):1205–53.
- [21] Ohe T, Shimomura K, Aihara N, Kamakura S, Matsuhisa M, Sato I, Nakagawa H, Shimizu A. Idiopathic sustained left ventricular tachycardia: clinical and electrophysiologic characteristics. *Circulation* 1988;77:560–8.
- [22] Gehi AK, Duong TD, Metz LD, Gomes JA, Mehta D. Risk stratification of individuals with the Brugada electrocardiogram: a meta-analysis. *J Cardiovasc Electrophysiol* 2006;17:577–83.
- [23] Kamakura S, Ohe T, Nakazawa K, Aizawa Y, Shimizu A, Horie M, Ogawa S, Okumura K, Tsuchihashi K, Sugi K, Makita N, Hagiwara N, Inoue H, Atarashi H, Aihara N, et al. Long-term prognosis of probands with Brugada-pattern ST-elevation in leads V1–V3. *Circ Arrhythm Electrophysiol* 2009;2:495–503.
- [24] Brugada P, Geelen P, Brugada R, Mont L, Brugada J. Prognostic value of electrophysiologic investigations in Brugada syndrome. *J Cardiovasc Electrophysiol* 2001;12:1004–7.
- [25] Brugada P, Brugada R, Mont L, Rivero M, Geelen P, Brugada J. Natural history of Brugada syndrome: the prognostic value of programmed electrical stimulation of the heart. *J Cardiovasc Electrophysiol* 2003;14:455–7.
- [26] Takagi M, Yokoyama Y, Aomuma K, Aihara N, Hiraoka M, for the Japan Idiopathic Ventricular Fibrillation Study (J-IVFS) Investigators. Clinical characteristics and risk stratification in symptomatic and asymptomatic patients with Brugada syndrome: multicenter study in Japan. *J Cardiovasc Electrophysiol* 2007;18:1244–51.
- [27] Sacher F, Probst V, Iesaka Y, Jacon P, Laborderie J, Mizon-Gerard F, Mabo P, Reuter S, Lamaison D, Takahashi Y, O'Neill MD, Garrigue S, Pierre B, Jaïs P, Pasquie JL, et al. Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: a multicenter study. *Circulation* 2006;114:2317–24.
- [28] Daubert JP, Zareba W, Hall WJ, Schuger C, Corsello A, Andrews ML, McNitt S, Huang DT, Moss AJ, MADIT II Study Investigators. Predictive value of ventricular arrhythmia inducibility for subsequent ventricular tachycardia or ventricular fibrillation in Multicenter Automatic Defibrillator Implantation Trial (MADIT) II patients. *J Am Coll Cardiol* 2006;47:98–107.